with the proviso that A is not [any of the ~~following~~ nucleotide sequences selected from a group consisting of] the nucleic acid sequence shown in SEQ ID NO:33, A is not the nucleic acid sequence shown in SEQ ID NO:35, A is not the nucleic acid sequence shown in SEQ ID NO:37, A is not the nucleic acid sequence shown in SEQ ID NO:39 and A is not the nucleic acid sequence shown in SEQ ID NO:41.

REMARKS

Claims 1-17, 30-31, 33-47, 60-61, 63-65, 69-71, and 75-77 were under consideration in the application. Claims 1-17, 33-47, 63-65, 69-71, and 77 have been amended. Accordingly, claims 1-17, 30-31, 33-47, 60-61, 63-65, 69-71, and 75-77 are currently pending. Support for the above amendments can be found in the claims as originally filed, as well as throughout the specification. Specifically, support for the amendments to claims 1, 9, 33, 40, and 77 can be found at least at pages 9, lines 11-21 and 11, lines 1-14. SEQ ID NO:s 18 and 22 were present in the application as filed and support for the recitation of "B7-1 or B7-2" in the claims can be found at least at page 2, lines 32-34.

No new matter has been added. For the Examiner's convenience, a copy of the claims as pending after amendment is provided in Appendix A.

Applicants further submit that the above amendments raise no new issues which would require further consideration and/or search by the Examiner.

Amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

The claims as pending are directed to nucleic acid molecules which are alternative splice forms of a transcript which encodes a B7-1 or B7-2 molecule. These B7-1 and B7-

2 nucleic acid molecules are naturally occurring variants of the nucleotide sequences shown in SEQ ID NO:18 or SEQ ID NO:22 which were not previously known in the art.

Independent claim 1 is drawn to a B7-1 or B7-2 nucleic acid molecule which comprises the structure A-B-C-D-E, where A encodes a B7-1 or B7-2 signal peptide domain, B encodes a B7-1 or B7-2 immunoglobulin variable region-like domain, C encodes a B7-1 or B7-2 immunoglobulin constant region-like domain, D a B7-1 or B7-2 transmembrane domain, and E encodes a B7-1 or B7-2 cytoplasmic domain which is not taught in the prior art, i.e., is not the mouse B7-1 cytoplasmic (cyt) I nucleic acid sequence shown in SEQ ID NO:25, is not the human B7-1 cytoplasmic (cyt) I nucleic acid sequence shown in SEQ ID NO:27, is not the mouse B7-2 cytoplasmic (cyt) I nucleic acid sequence shown in SEQ ID NO:29 and is not the human B7-2 cytoplasmic (cyt) I nucleic acid sequence shown in SEQ ID NO:31.

Independent claim 9 is drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 and which is an alternative splice form of a transcript of the a B7-1 or B7-2 molecule gene which has at least one first exon encoding a prior art B7-1 or B7-2 first cytoplasmic domain comprising a nucleotide sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29 and SEQ ID NO:31 (the prior art mouse and human B7-1 and B7-2 cyt domains), and at least one second exon encoding a B7-1 or B7-2 second cytoplasmic domain.

Independent claim 15 is drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising the specific nucleotide sequence shown in SEQ ID NO:1. SEQ ID NO: 1 is an alternative splice form of a transcript which encodes a mouse B7-1 molecule in which exon 5 of the prior art, cyt I, is deleted.

Independent claim 16 is drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising a nucleotide sequence shown in SEQ ID NO:3. SEQ ID NO: 3 is an alternative splice form of a transcript which encodes a mouse B7-1 molecule in which exon 5 of the prior art, cyt I, and a novel cyt II domain are both present.

Independent claim 17 is drawn to an isolated nucleic acid molecule encoding a cytoplasmic domain derived from a B7-1 or B7-2 protein which binds CD28 or CTLA4, the nucleic acid comprising the novel B7-1 cyt II nucleotide sequence shown in SEQ ID NO:4.

Independent claim 33 is drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising a contiguous nucleotide sequence which is an alternative splice form of a transcript of a B7-1 or B7-2 T cell costimulatory molecule gene, the nucleotide sequence represented by a formula A-B-C-D-E, wherein A encodes a B7-1 or B7-2 signal peptide domain, B encodes a B7-1 or B7-2 immunoglobulin variable region-like domain, C encodes a B7-1 or B7-2 immunoglobulin constant region-like domain, D, which may or may not be present, encodes a B7-1 or B7-2 transmembrane domain, and E, which may or may not be present, encodes a B7-1 or B7-2 cytoplasmic domain, wherein A is not a B7-1 or B7-2 nucleic acid molecule encoding a signal peptide domain as taught in the prior art, i.e., is not the mouse B7-1 signal peptide nucleic acid sequence shown in SEQ ID NO:33, is not the human B7-1 signal peptide nucleic acid sequence shown in SEQ ID NO:35, is not the mouse B7-2 signal peptide nucleic acid sequence shown in SEQ ID NO:37, is not the human B7-2 h1A signal peptide nucleic acid sequence shown in SEQ ID NO:39 and A is not the human B7-2 h1B signal peptide nucleic acid sequence shown in SEQ ID NO:41.

Independent claim 40 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 and which is an alternative splice form of a

transcript of a B7-1 or B7-2 T cell costimulatory molecule gene having at least one first exon encoding a B7-1 or B7-2 first signal peptide domain comprising a prior art B7-1 or B7-2 nucleotide sequence selected from the group consisting of a nucleotide sequence of SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37 SEQ ID NO:39 and SEQ ID NO:41, and at least one second exon encoding a B7-1 or B7-2 second signal peptide domain, wherein the isolated nucleic acid comprises a nucleotide sequence encoding the second signal peptide domain.

Independent claim 42 is drawn to an isolated nucleic acid molecule which encodes a B7-1 or B7-2 protein which binds to CD28 or CTLA4, wherein the nucleic acid molecule comprises a nucleotide sequence shown in SEQ ID NOs: 4 (encoding a mouse B7-1 cyt II domain) and 14 (encoding a mouse B7-1 m1B domain).

Independent claim 46 is drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising a nucleotide sequence shown in SEQ ID NO:12 (comprising a nucleic acid molecule encoding a novel mouse m1B domain).

Independent claim 47 is drawn to an isolated nucleic acid molecule encoding a signal peptide domain derived from a B7-1 or B7-2 protein which binds CD28 or CTLA4, the nucleic acid comprising a novel mouse B7-2 m1B nucleotide sequence shown in SEQ ID NO:14.

Independent claim 63 is drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein comprising a contiguous nucleotide sequence derived from at least one B7-1 or B7-2 T cell costimulatory molecule gene, the nucleotide sequence, wherein the immunoglobulin variable region-like domain has been deleted.

Independent claim 69 is drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein comprising a contiguous nucleotide sequence derived from at least

one B7-1 or B7-2 T cell costimulatory molecule gene, wherein the immunoglobulin constant region-like domain is deleted.

Independent claim 77 is a generic claim which embraces the species of claims 1 and 33 (as set forth above) in the alternative.

These novel nucleic acid molecules, as well as those claimed in the dependent claims pending in the application, were not heretofore known in the prior art.

Rejection of claims 1-8, 33-39, and 77 Under 35 U.S.C. §112, first paragraph

Claims 1-8, 33-39 and 77 have been rejected under 35 U.S.C. § 112, first paragraph. It is the Examiner's position that "[t]he specification as originally filed does not provide support for the invention as now claimed: [i.e.,] the recitation of 'is not any of the following' in claims 1, 33 and 77." This rejection respectfully traversed.

It is the Examiner's position that:

> Applicant's amendment, filed 12/22/97 (Paper No. 10) indicates support can be found in claims as originally filed as well as throughout the specification. While the specification and original claims provide written description for the recited negative limitations as they read on the members of the Markush claims, applicant has not provided sufficient guidance and direction for the negative limitation to read 'any of the following nucleotide sequences', that is, the combination of all of the members of the Markush claims. . . . The specification as filed does not provide a written description or set forth the metes and bounds of the negative limitation. The specification does not provide sufficient blazemarks nor direction for the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

This rejection is respectfully traversed.

It is Applicant's position that there is support in the specification as filed to exclude the prior art sequences which are specifically excluded from claims 1, 33, and 77. For example, at least at page 9, lines 9-21, Applicants teach that a first cytoplasmic domain of a B7-1 or B7-2 T cell costimulatory molecule is shown in any one of SEQ ID NOs: 25, 27, 29, and 31. Applicants further teach that in a preferred embodiment, an alternatively spliced form of a costimulatory molecule "does not comprise a nucleotide sequence encoding a first cytoplasmic domain (i.e., the nucleic acid comprises an alternative splice form of a transcript of the gene in which the exon encoding the first cytoplasmic domain, e.g., exon 5, has been excised from the transcript)." Similarly, at least at page 11, lines 1-14, Applicants teach that a first signal domain sequence is shown in any one of SEQ ID NOs: 33, 35, 37, 39, and 41. Applicants teach that in a preferred embodiment, an alternatively spliced form of a costimulatory molecule "does not comprise a nucleotide sequence encoding a first signal domain (i.e., the nucleic acid comprises an alternative splice form of a transcript of the gene in which the exon encoding a first signal domain has been excised from the transcript)."

Thus, it is Applicants position that the negative limitations in claims 1, 33, and 77 are fully supported in the specification as filed. In addition, Applicants have amended claims 1, 33, and 77 to eliminate the Markush grouping and to make it clear that Applicants intended to exclude the prior art sequences from the claimed costimulatory molecules. Therefore, Applicants respectfully request that the rejection of claims 1-8, 33-39 and 77 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Rejection of claims 1-15, 17, 30-31, 33-45, 60-61, 63, 69, and 75-77 Under 35 U.S.C. §112, first and second paragraphs

Claims 1-15, 17, 30-31, 33-45, 60-61, 63, 69, 75-77 have been rejected under 35 U.S.C. § 112, first and second paragraphs. It is the Examiner's position that the claims are indefinite in that:

> they only describe the 'isolated nucleic acids encoding a protein which binds CD28 or CTLA-4' by reciting various elements (e.g. first exon, second exon, third exon, fourth exon, fifth exon), a proviso that certain elements are not any of the following nucleotide sequences set forth in a Markush, or the nucleotide sequence is derived from co-stimulatory molecule gene. While these characteristics may have some notion of the specificity of the nucleic acids, these claims lack sufficient structural information or defining characteristics which distinctly claims the isolated nucleic acids, including the various elements (e.g. exons, domains). Claiming biochemical molecules by generic terms such as exons, domains, immunoglobulin variable region-like or by particular name given to the encoded protein (i.e. B7-1, B7-2) fails to distinctly claim what that isolated nucleic acid is and what it is made up of. Also, it is noted that it is not clear what the various exons or domains should be (e.g. second cytoplasmic domain in claim 9).

This rejection is respectfully traversed.

It is Applicant's position that amended claims 1-15, 17, 30-31, 33-45, 60-61, 63, 69, 75-77 are definite in that they are all directed to novel nucleic acid molecules which are naturally occurring variants of the nucleotide sequence shown in SEQ ID NO:18 or SEQ ID NO:22. The instant costimulatory molecules are alternative splice forms of the prior art B7-1 and/or B7-2 molecules. It is Applicant's position that the nucleic acid sequences and exon structure of the prior art non-alternatively spliced B7-1 and B7-2 molecules are taught by Applicants in the instant specification and were well known in

the art at the time of filing the application. Applicants further contend that the protein domains of the B7-1 and B7-2 molecules were also taught in the specification (see, e.g., page 16 of the application where the amino acid positions of certain domains are set forth) and were known in the art. Applicants refer to the Freeman, Selvakumar, and Azuma references cited by the Examiner.

Since the claims as pending are drawn to naturally occurring variants of B7-1 and B7-2 molecules and refer to exons and domains of B7-1 and B7-2 molecules which were well known in the art, it is Applicant's position that the claims provide sufficient structural information and defining characteristics which would be readily understood by one of ordinary skill in the art. With specific regard to claim 9, Applicants note that claim 9 has been amended to recite that the second cytoplasmic domain is a B7-1 or B7-2 second cytoplasmic domain.

It is further the Examiner's position that:

> "[t]he scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the ill-defined number of nucleic acids broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the instant specification discloses a limited number of alternative spliced forms of co-stimulatory molecules. . . . Also the claims recites negative limitations with respect to other known nucleic acids encoding B7-1 or B7-2, however there is insufficient guidance and written description for the breadth of the claimed nucleic acids. Predicting structural determinations to ascertain functional aspects of the nucleic

> acids to encode functional protein which bind CD28 and CTL-4 and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

This rejection is respectfully traversed.

The pending claims are drawn to alternate splice variants of B7-1 and B7-2 molecules. As set forth above, the claims require that the subject alternatively spliced forms of B7-1 or B7-2 molecules meet certain structural limitations. In addition to meeting the structural requirements of the claims, the subject nucleic acid molecules must encode a functional B7-1 or B7-2 molecule which binds to CD28 or CTLA4. Thus, the claims only embrace B7-1 and B7-2 nucleic acid molecules which encode functional T cell costimulatory molecules and do not read on inoperative species.

Furthermore, Applicants provide sufficient guidance to enable one of ordinary skill in the art to determine whether a given nucleic acid molecule encodes a B7-1 or B7-2 molecule with costimulatory activity. For example, at least at page 30 Applicants teach that the novel T cell costimulatory molecules of the invention can be expressed in membrane bound form by expressing the molecule in a host cell (e.g., by transfecting the host cell with a recombinant expression vector encoding the molecule). Applicants teach that to trigger a costimulatory signal, T cells are contacted with the cell expressing the costimulatory molecule, preferably together with a primary activation signal (e.g., MHC-associated antigenic peptide, anti-CD3 antibody, phorbol ester etc.). Activation of a T cell can be assayed by standard procedures, for example by measuring T cell proliferation or cytokine production. The methods taught by Applicants, as well as other methods of measuring costimulatory signals known in the art, could readily be used to determine whether a nucleic acid molecule functions according to the limitations of the claim without undue experimentation.

It is further the Examiner's position that:

> the claims are not even limited to clearly defined number of nucleic acids encoding CD28-CTLA-4-binding proteins, but further extend to an ill-defined number of species which share one or more functional or structural characteristics with the B7-1 or B7-2 molecules attributed to in the specification. As the specification does not teach how to make or use a number of species that would be commensurate in scope with the claims, it is found that it would require undue experimentation practice the invention in a manner commensurate in scope with the claims.

This rejection is respectfully traversed.

It is Applicants position that, given Applicants teachings, it would not require undue experimentation to practice the invention in a manner commensurate in scope with the claims, which recite the structural and functional limitations as set forth above. For example, beginning at page 14, Applicants teach that cDNAs encoding the costimulatory molecule can be amplified by reverse transcriptase-polymerase chain reaction (RT-PCR) using oligonucleotide primers specific for the costimulatory molecule gene. The amplified cDNAs can then be subcloned into a plasmid vector and sequenced by standard methods. Oligonucleotide primers for RT-PCR can be designed based upon previously disclosed nucleotide sequences of costimulatory molecules (see Freeman, G.J. et al., (1991) *J. Exp. Med.* 174:625-631 for mB7-1; Freeman, G.J. et al., (1989) *J. Immunol.* 143:2714-2722 for hB7-1; Freeman, G.J. et al., (1993) *J. Exp. Med.* 178:2185-2192 for mB7-2; and Freeman, G.J. et al., (1993) *Science* 262:909-911 for hB7-2; nucleotide sequences are shown in SEQ ID NOS: 16, 18, 20, 22 and 24). For analyzing the 5' or 3' ends of mRNA transcripts, cDNA can be prepared using a 5' or 3' "RACE" procedure ("rapid amplification of cDNA ends) as described in the Examples. Alternative to amplifying specific cDNAs, a cDNA library can be prepared from a cell line which expresses the costimulatory molecule and screened with a probe containing all or a portion of the nucleotide sequence encoding the costimulatory molecule.

Applicants further teach that individual isolated cDNA clones encoding a T cell costimulatory molecule can then be sequenced by standard techniques, such as dideoxy sequencing or Maxam-Gilbert sequencing, to identify a cDNA clone encoding a T cell costimulatory molecule having a novel structural domain. A novel structural domain can be identified by comparing the sequence of the cDNA clone to the previously disclosed nucleotide sequences encoding T cell costimulatory molecules (e.g., sequences shown in SEQ ID NO: 16, 18, 20, 22 and 24). Once a putative alternative structural domain has been identified, the nucleotide sequence encoding the domain can be mapped in genomic DNA to determine whether the domain is encoded by a novel exon.

Alternatively, Applicants teach that a novel structural domain for T cell costimulatory molecules can be identified in genomic DNA by identifying a novel exon in the gene encoding the T cell costimulatory molecule. A novel exon can be identified as an open reading frame flanked by splice acceptor and splice donor sequences. Genomic clones encoding a T cell costimulatory molecule can be isolated by screening a genomic DNA library with a probe encompassing all or a portion of a nucleotide sequence encoding the costimulatory molecule (e.g., having all or a portion of a nucleotide sequence shown in SEQ ID NO: 16, 18, 20, 22 and 24). For costimulatory molecules whose genes have been mapped to a particular chromosome, a chromosome-specific library rather than a total genomic DNA library can be used. For example, hB7-1 has been mapped to human chromosome 3 (see Freeman, G.J. et al. (1992) *Blood* 79:489-494; and Selvakumar, A. et al. (1992) *Immunogenetics* 36:175-181. Genomic clones can be sequenced by conventional techniques and novel exons identified. A probe corresponding to a novel exon can then be used to detect the nucleotide sequence of this exon in mRNA transcripts encoding the costimulatory molecule (e.g., by screening a cDNA library or by PCR).

Applicants further teach that a more preferred approach for identifying and isolating nucleic acid encoding a novel structural domain of a T cell costimulatory molecule is by "exon trapping". Exon trapping is a technique that has been used successfully to identify and isolate novel exons (see e.g. Duyk, G.M. et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:8995-8999; Auch, D. and Reth, M. (1990) *Nucleic Acids Res.* 18:6743-6744; Hamaguchi, M. et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:9779-9783; and Krizman, D.B and Berget, S.M. (1993) *Nucleic Acids Res.* 21:5198-5202). The approach of exon trapping can be applied to the isolation of exons encoding novel structural domains of T cell costimulatory molecules, such as a novel alternative cytoplasmic domain of human B7-1, as described in Example 5.

Thus, it is Applicants position that the pending claims are definite and are fully enabled by the specification as filed. Therefore, Applicants respectfully request that the rejection of claims 1-15, 17, 30-31, 33-45, 60-61, 63, 69, 75-77 under 35 U.S.C. § 112, first and second paragraphs be reconsidered and withdrawn.

Rejections Under 35 U.S.C.§ 102(b)

The Examiner has made the following rejections under 35 U.S.C. § 102(b):

Rejection of claims 1-7, 9-16, 30-31, 33-35, 40-41, 63-65, 69-71, and 75-77 as being anticipated by Freeman et al. (J. Exp. Med. 174:625-631,1991);

Rejection of claims 1-4, 6-7, 9-12, 14-16, 30-31, 33-35, 40-41, 63-65, 69-71, and 75-77 as being anticipated by Selvakumar et al. (Immunogenetics 36:175-181, 1992);

Rejection of claims 1-5, 7, 9-13, 15-16, 30-31, 33-35, 40-41, 63-65, 69-71, and 75-77 as being anticipated by Selvakumar et al. (Immunogenetics 38:292-295, 1993);

Rejection of claims 1-4, 6-7, 9-12, 14-16, 30-31, 33-35, 40-41, 63-65, 69-71, and 75-77 as being anticipated by Freeman et al. (JI 143:2714-2722,1989);

Rejection of claims 1-3, 33-37, 39-44, 46-47, 60-61, 63, 69, and 75-77 as being anticipated by Freeman et al. (J. Exp. Med. 178:2185-2192, 1993);

Rejection of claims 1-3, 33-36, 38-43, 45-46, 60-61, 63, 69, and 75-55 102(a) as being anticipated by Freeman et al. (Science 262: 909-911,1993); and

Rejection of claims 1-3, 33-36, 38-43, 45-46, 60-61, 63, 69, and 75-77 as being anticipated by Azuma et al. (Nature 336:76-77, 1993).

These rejections are respectfully traversed.

The Teachings of the References

The teachings of Freeman et al. (1991) are limited to the cloning of the mouse B7-1 cDNA. Freeman et al. disclose that the mouse B7 homologue exhibits structural features similar to the human gene and is composed of a signal peptide, Ig-V and Ig-C domains, a transmembrane region and a cytoplasmic domain.

Selvakumar et al. (1992) disclose the genomic organization of the human gene encoding B7. In particular, Selvakumar et al. disclose that the gene has six exons: exon 1 is not translated, exon 2 contains the signal peptide domain, the third and fourth exons correspond to two Ig-like domains, the fifth exon encodes the transmembrane domain and the sixth exon encodes the cytoplasmic domain.

Selvakumar et al. (1993) disclose the genomic organization of the mouse B7 gene. In particular, Selvakumar et al. disclose that the first exon contains the 5' untranslated region and signal peptide, the second and third exons correspond to the extracellular Ig-V-like and Ig-C-like domains, the fourth exons corresponds to the transmembrane region, and the fifth exon contains the cytoplasmic tail.

Freeman et al. (1989) disclose the cloning of human B7-1. Freeman et al. disclose that the predicted protein has a signal peptide, an extracellular domain, a hydrophobic transmembrane region and a cytoplasmic tail.

Freeman et al. (1993a) disclose the cloning of a mouse B7-2 cDNA. Freeman et al. discloses the amino acid sequence of the mouse B7-1, human B7-1, mouse B7-2, and human B7-2 proteins.

Freeman et al. (1993b) disclose the cloning of a human B7-2 cDNA. Freeman et al. discloses the amino acid sequence of the mouse B7-1, human B7-1, and human B7-2 proteins.

Azuma et al. (1993) disclose the cloning of a human B7-2 cDNA. Azuma discloses the amino acid sequence of the mouse B7-1, human B7-1 and human B7-2 proteins.

It is Applicants' position that the pending claims, which are drawn to naturally occurring variant of the nucleotide sequence shown in SEQ ID NO:18 or SEQ ID NO:22 are not anticipated by the art of record.

Claims 1, 15, 77, and the claims which depend therefrom are drawn to isolated nucleic acid molecules encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising a contiguous nucleotide sequence which is an alternative splice form of a transcript of a B7-1 or B7-2 molecule and do not comprise a nucleotide sequence encoding the prior art B7-2 or B7-2 cytoplasmic domains.

Claim 1 is drawn to an nucleic acid molecule encoding a B7-1 or B7-2 molecule which binds to CD28 or CTLA4 and has a cytoplasmic domain which ***does not*** comprise the nucleic acid sequence shown in SEQ ID NO: 25, ***does not*** comprise the nucleic acid sequence shown in SEQ ID NO: 27, ***does not*** comprise the amino acid sequence shown in SEQ ID NO:29, and ***does not*** comprise the nucleic acid sequence shown in SEQ ID NO: 31. SEQ ID NO: 25, 27, 29, and 31 correspond to the nucleotide sequences which encode

the cytoplasmic domain of mouse B7-1, human B7-1, mouse B7-2, and human B7-2 proteins, respectively.

Independent claim 77 is a generic claim which embraces the species of claim 1.

Independent claim 15 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising the specific nucleotide sequence shown in SEQ ID NO:1. SEQ ID NO: 1 is an alternative splice form of a transcript which encodes a mouse B7-1 molecule in which exon 5 of the prior art, cyt I, is deleted.

The teachings of the prior art of record do not include the claimed novel nucleic acid molecules which lack the nucleotide sequences shown in SEQ ID NO: 25, 27, 29, or 31. It is respectfully requested that the Examiner refer to the specific teachings within the cited reference(s) being relied upon as a basis for the above rejection if the rejection is going to be maintained.

Claims 9, 16 and the claims which depend therefrom are drawn to an isolated nucleic acid molecule encoding a B7-1 or B7-2 protein which has two cytoplasmic domains.

Independent claim 9 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 and which is an alternative splice form of a transcript of the a B7-1 or B7-2 molecule gene which has at least one first exon encoding a prior art B7-1 or B7-2 first cytoplasmic domain comprising a nucleotide sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29 and SEQ ID NO:31 (the prior art mouse and human B7-1 and B7-2 cyt domains), and at least one second exon encoding a B7-1 or B7-2 second cytoplasmic domain.

Independent claim 16 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising a nucleotide sequence shown in SEQ ID NO:3. SEQ ID NO: 3 is an alternative splice form of a transcript which encodes a

mouse B7-1 molecule in which exon 5 of the prior art, cyt I, and a novel cyt II domain are both present.

The teachings of the prior art of record do not include the claimed novel nucleic acid molecules which comprise two cytoplasmic domains. It is respectfully requested that the Examiner refer to the specific teachings within the cited reference(s) being relied upon as a basis for the above rejection if the rejection is going to be maintained.

Claims 33 and 77 and the claims which depend therefrom are drawn to isolated nucleic acid molecules encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising a contiguous nucleotide sequence which is an alternative splice form of a transcript of a B7-1 or B7-2 which do not comprise a nucleotide sequence encoding the prior art signal peptide domains.

Claim 33 is drawn to a nucleic acid molecule encoding a B7-1 or B7-2 molecule which binds to CD28 or CTLA4 and has a nucleotide sequence encoding a signal peptide which ***does not*** comprise the nucleic acid sequence shown in SEQ ID NO: 33, ***does not*** comprise the amino acid sequence shown in SEQ ID NO: 35, ***does not*** comprise the amino acid sequence shown in SEQ ID NO:37, and ***does not*** comprise the amino acid sequence shown in SEQ ID NO: 39, and ***does not*** comprise the amino acid sequence shown in SEQ ID NO: 41,. SEQ ID NO: 33, 35, 37, 39 and 41 correspond to the nucleotide sequences which encode the signal peptides of mouse B7-1, human B7-1, mouse B7-2, and human B7-2 h1A and h1B proteins, respectively.

Independent claim 77 is a generic claim which embraces the species of claim 33.

The teachings of the prior art of record do not include the claimed novel nucleic acid molecules which lack the nucleotide sequences shown in SEQ ID NO: 33, 35, 37, 39 and 41. It is respectfully requested that the Examiner refer to the specific teachings

within the cited reference(s) being relied upon as a basis for the above rejection if the rejection is going to be maintained.

Claims 40 and the claims which depend therefrom are drawn to nucleic acid molecules which encode proteins which comprise two signal peptide domains.

Independent claim 40 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 and which is an alternative splice form of a transcript of a B7-1 or B7-2 T cell costimulatory molecule gene having at least one first exon encoding a B7-1 or B7-2 first signal peptide domain comprising a prior art B7-1 or B7-2 nucleotide sequence selected from the group consisting of a nucleotide sequence of SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37 SEQ ID NO:39 and SEQ ID NO:41, and at least one second exon encoding a B7-1 or B7-2 second signal peptide domain, wherein the isolated nucleic acid comprises a nucleotide sequence encoding the second signal peptide domain.

The teachings of the prior art of record do not include the claimed novel costimulatory molecules which comprise two signal peptide domains. It is respectfully requested that the Examiner refer to the specific teachings within the cited reference(s) being relied upon as a basis for the above rejection if the rejection is going to be maintained.

Claims 17, 42, 46, and 47 and the claims which depend therefrom are drawn to nucleic acid molecules comprising novel nucleotide sequences.

Independent claim 17 is drawn to an isolated nucleic acid molecule encoding a cytoplasmic domain derived from a B7-1 or B7-2 protein which binds CD28 or CTLA4, the nucleic acid comprising the novel B7-1 cyt II nucleotide sequence shown in SEQ ID NO:4.

Independent claim 42 is drawn to an isolated nucleic acid which encodes a B7-1 or B7-2 protein which binds to CD28 or CTLA4, wherein the nucleic acid molecule comprises a nucleotide sequence shown in SEQ ID NOs: 4 (encoding a mouse B7-1 cyt II domain) and 14 (encoding a mouse B7-1 m1B domain).

Independent claim 46 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein which binds CD28 or CTLA4 comprising a nucleotide sequence shown in SEQ ID NO:12 (comprising a nucleic acid molecule encoding a novel mouse m1B domain).

Independent claim 47 is drawn to an isolated nucleic acid molecule encoding a signal peptide domain derived from a B7-1 or B7-2 protein which binds CD28 or CTLA4, the nucleic acid shown in SEQ ID NO:14 (comprising a novel mouse B7-2 m1B nucleotide sequence).

The teachings of the prior art of record do not include the claimed novel costimulatory molecules which comprise these novel nucleotide sequences. It is respectfully requested that the Examiner refer to the specific teachings within the cited reference(s) being relied upon as a basis for the above rejection if the rejection is going to be maintained.

Claims 63 and 69 and the claims which depend therefrom are drawn to nucleic acid molecules not taught in the prior art which comprise deletions of certain costimulatory molecule domains

Independent claim 63 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein comprising a contiguous nucleotide sequence derived from at least one B7-1 or B7-2 T cell costimulatory molecule gene, the nucleotide sequence represented by a formula, wherein the immunoglobulin variable region-like domain has been deleted.

Independent claim 69 is drawn to an isolated nucleic acid encoding a B7-1 or B7-2 protein comprising a contiguous nucleotide sequence derived from at least one B7-1 or

B7-2 T cell costimulatory molecule gene, wherein the immunoglobulin constant region-like domain is deleted.

The teachings of the prior art of record do not include the claimed novel costimulatory molecules which comprise deletions of certain costimulatory molecule domains. It is respectfully requested that the Examiner refer to the specific teachings within the cited reference(s) being relied upon as a basis for the above rejection if the rejection is going to be maintained.

For all of the foregoing reasons, Applicants respectfully request that the above rejections under 35 USC §102(b) be reconsidered and withdrawn.

Rejection of claims 1-6, 9-16, 30-31, 3-31, 43-47, 60-61, 63-65, 69-71, and 75-77 Under 35 U.S.C. §103

Claims 1-6, 9-16, 30-31, 3-31, 43-47, 60-61, 63-65, 69-71, and 75-77 have been rejected as being obvious over any of Freeman et al. (J. Exp. Med. 174:625-631, 1991), Selvakumar et al. (Immunogenetics 26:175-181, 1992), Selvakumar et al. (Immunogenetics 38:292-195, 1993), Freeman et al. (J. Immunol. 143:2714-1722, 1989), Freeman et al. (J. Exp. Med. 178:2185-2192, 1993). Freeman et al. (Science 262:909-911, 1993), or Azuma et al. (Nature 366:76-77, 1993). This rejections is respectfully traversed.

The Examiner characterizes the prior art as differing "from the claimed invention by not all of the allelic variants and signal sequences encompassed by the claims." It is the Examiner's position that:

> it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a various signal sequences for expression of the protein for various uses, including large volumes and bacterial cell expression. In addition, the ordinary artisan would have expected and would have expected to obtain minor modifications

> (substitutions, additions, deletions or insertions) for example due to allelic variation. A person of ordinary skill in the art would have been motivated to do so for secretion of the protein from the bacterial cell. Therefore it an isolated protein expressed by a construct not having the above listed signal sequences would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made in view of the above cited references and the contemporary knowledge in the art at the time the invention was made.

Applicants respectfully submit that the references fail to teach or suggest the claimed variants of B7-1 or B7-2 molecules.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success ***must be founded in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

The Examiner has failed to establish a *prima facie* case of obviousness in the instant obviousness rejection since the cited references fails to teach or suggest ***any*** modification to the prior art B7 molecules, let alone the spice variants described by Applicants. Applicants submit that the teachings relied on by the Examiner in the instant case are insufficient to establish the obviousness of the claimed invention absent some

teaching or suggestion in the art to modify the teachings of those references to arrive at the claimed invention. The Examiner has failed to point to any suggestion that it would be desirable to modify the prior art proteins which bind to CD28 or CTLA4 at the time the invention was made in ***any*** way, let alone by modifying them as taught by Applicants. Accordingly, a person of skill in the art at the time of the invention would not have been motivated to make the claimed invention in view of the cited references.

Thus, Applicants submit that claims 1-6, 9-16, 30-31, 3-31, 43-47, 60-61, 63-65, 69-71, and 75-77 are patentable and request that the rejection under 35 USC § 103 be withdrawn.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that none of the art of record teaches or suggests the novel forms of costimulatory molecules as presently claimed. The amended claims exclude the prior art costimulatory molecules, thus, Applicants respectfully submit that claims 1-17, 30-31, 33-47, 60-61, 63-65, 69-71, and 75-77 are patentable.

If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call Applicants' Agent at the number provided below.

Respectfully submitted,

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